

## Experience with Heterotopic Heart Transplantation in Patients with Elevated Pulmonary Vascular Resistance. Late Follow-up

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### Abstract

**Background:** Along the past few years the number of papers on heterotopic cardiac transplant has been very scarce in the medical literature, including at the international level; this is particularly true in reference to the long term follow-up of these patients and the reason which led to the presentation of our report.

**Objective:** To report the initial clinical experience and late evolution of 4 patients undergoing heterotopic heart transplantation, indications for this procedure and its major complications.

**Methods:** The surgeries were performed between 1992 and 2001, and all had as indication for heterotopic transplantation the PVR, which ranged from 4.8 WU to 6.5WU, with a transpulmonary gradient above 15mmHg. In the 3rd patient, a direct anastomosis between the pulmonary arteries was performed without the use of a prosthetic tube, and a mitral valvuloplasty and a LV aneurysmectomy were performed in the native heart.

The immediate immunosuppressive regimens were double, with cyclosporine and azathioprine in the first 3 patients, and cyclosporine and mycophenolate mofetil in the 4th patient.

**Results:** One immediate death occurred from graft failure, one death occurred after 2 ½ years, from endocarditis in an intraventricular thrombus in the native heart, and a third death occurred 6 years after transplantation, from post-operative complications of the aortic valve surgery in the native heart. The remaining patient is well, 15 years after the transplantation. This patient is in functional class II (NYHA), 6 years after a surgical occlusion of the native heart aortic valve.

**Conclusion:** Heterotopic heart transplantation results are inferior to those of orthotopic heart transplantation because they present higher RVP. The intraventricular thrombi, in the native heart, which require prolonged anticoagulation, and aortic valve complications, also in the native heart, may require surgical treatment. However, a patient's 15-year survival has demonstrated a long-term effectiveness of this option for selected patients. (*Arq Bras Cardiol* 2010;94(2): 244-249)

**Key Words:** Heart transplantation; hypertension, pulmonary / complications; follow-up studies.

### Introduction

The high pulmonary vascular resistance (PVR) which occurs in the final stage of cardiomyopathies has been a major obstacle to the performance of orthotopic heart transplantation, due to the risk of early failure of the right ventricle (RV) of the transplanted organ, limiting its use in patients with PVR below 5 Wood units (WU)<sup>1,2</sup>, or 4 Wood units, currently in preference.

The clinical application of the heterotopic heart transplantation (HetTrx) by Barnard, in 1974, increased the possibility of performing cardiac transplantation in patients with a PVR above 4 WU<sup>3,4</sup>, and it was widely used by the South African Group, especially with the additional argument that in case of graft failure, in a scenario when cyclosporine

was not yet available, the patients would survive thanks to the native organ. Among other indications of this procedure, we can mention its use in potentially reversible ventricular dysfunctions, and in cases of size disproportion between donor and recipient. This last condition is a possibility, particularly in patients with ischemic cardiomyopathy, even with the possibility of conventional surgical treatment, when the heterotopic graft could be implanted for greater security in the early evolution of these patients<sup>3-5</sup>.

The aim of this article is to report the experience of four procedures performed in our department, emphasizing the details of the procedures, a modification in the original operative technique, and the later follow-up of the patients, up to 15 years.

### Methods

Between August 1988 and December 2007, 222 heart transplants were performed in our group in the Hospital Beneficência Portuguesa of São Paulo, including 6 re-

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transplants. In this experiment, in 4 patients, we opted for the heterotopic transplantation, according to the marked increase of PVR. The clinical characteristics of these 4 patients are described in Table 1, which emphasizes the significantly high levels of PVR.

From a clinical perspective, the patients had severe ischemic cardiomyopathy. All of them had extensive myocardial infarction, and their coronary arteries were not suitable to surgical treatment. They were in the ICU, receiving inotropic and vasodilator drugs, and were on the waiting list for heart transplantation. The first patient had undergone a previous myocardial revascularization surgery, with occlusion of the grafts, and the last patient had undergone coronary angioplasty on two occasions prior to the transplantation. In the latter patient, who underwent surgery in November 2001, in addition to a graft implant in a heterotopic position, the correction of a left ventricle aneurysm and a valvuloplasty of the mitral valve were performed. The other two patients were also in functional class IV (NYHA), and they had been frequently admitted to the ICU to receive vasodilator and inotropic drugs intravenously.

The surgical procedure was carried out with distant donor hearts in patients 1, 3 and 4, and with the heart from a donor in the adjacent room in patient 2. The donor organs were removed by sectioning the aorta above the brachiocephalic trunk and the pulmonary artery (PA) in the proximal part of the pulmonary branches. For myocardial protection, we used the St. Thomas cardioplegic solution, with antegrade infusion via native aortic valve in the heart of the receiver, except in the last case, in which we used retrograde coronary sinus infusion. In the donor heart we also used the antegrade cardioplegia administered via aortic infusion. We associated topical hypothermia by the immersion of the organs in cold Ringer's solution, and by packaging them for local or distant transportation. In the heart of the receiver, myocardial protection was performed with a cold blood cardioplegic solution.

The implantation surgical techniques were similar in the first two cases - the pulmonary artery of the donor heart was connected to the trunk of the native PA, using a bovine pericardium graft to facilitate the anastomosis. In patients 3 and 4 the original technique was used, with a direct anastomosis of the donor's PA to the right branch of the receiver's PA,

without any interposition graft, because the distance between them was much shorter<sup>5</sup>. To make this procedure feasible, the superior vena cava of the receiver was transected near the right atrium (RA), its lower end was sutured and its upper end was mobilized, fully exposing the right branch of the PA. To make this possible, we needed a wide dissection of the donor's pulmonary artery and its left branch, when the organ was removed. After the anastomoses of the left atria and the PAs were performed, the upper end of the superior vena cava of the receiver was anastomosed to the superior vena cava of the donor. Another right atrial connection was made in the lower portion of the receiver RA, near the interatrial septum, allowing the venous return of the receiver to reach the donor RA. The long ascending aorta of the donor was anastomosed as far as possible from the ascending aorta of the recipient, so as to facilitate the access to the PA in case of bleeding.

As an external pacemaker, temporary electrodes were placed in the RA of both hearts and in the RV of the transplanted heart, enabling a synchronized cardiac pacing through a sequential pacemaker, connecting the atrial poles to the atrial electrodes of the native heart (of higher frequency) and the atrial electrodes of the transplanted heart to the ventricular poles of the pacemaker. Thus, the pacemaker feels the P-wave of the native heart and, after an adjustable pause, stimulates the atrium of the transplanted heart, producing synchronized beats of both hearts, in the same logical sequence of the intra-aortic balloon which is important in optimizing the cardiac output in the first postoperative days<sup>6-8</sup>. After discharge from the ICU and the removal of epicardial wires of the pacemaker, there was no more electrical synchronization between the two hearts; however, a spontaneous tendency to an equalization of the heart beats occurred, which could be attributed to the lower adrenergic stimulation provided by an improved cardiac output, due to the implanted heart. (Figure 1)

Initially the immunosuppressive regimen was double, with cyclosporine and azathioprine in the first 3 patients, and cyclosporine and mycophenolate mofetil in the 4th patient. We conducted weekly biopsy controls in the first month, then fortnightly over the following 2 months, and after that, we conducted myocardial mapping with Gallium and echocardiogram to control rejection. The first patient had two episodes of significant myocardial rejection, which was

**Table 1 – Preoperative clinical characteristics**

Patient	Age	Diagnosis	Pulmonary artery pressure					PVR (WU)
			Systolic	Diastolic	Mean	Capilar	Transpulmonary gradient	
1	51	Ischemic cardiomyopathy	55	28	38	23	15	4.8
2	51	Same	57 <sup>a</sup> 65 <sup>b</sup>	30 <sup>a</sup> 34 <sup>b</sup>	41 <sup>a</sup> 44 <sup>b</sup>	27 <sup>a</sup> 28 <sup>b</sup>	14 <sup>a</sup> 16 <sup>b</sup>	4.3 <sup>a</sup> 5.3 <sup>b</sup>
3	41	Same	60 <sup>a</sup> 85 <sup>b</sup>	37 <sup>a</sup> 38 <sup>b</sup>	46 <sup>a</sup> 53 <sup>b</sup>	25 <sup>a</sup> 27 <sup>b</sup>	20 <sup>a</sup> 26 <sup>b</sup>	5.5 <sup>a</sup> 7.0 <sup>b</sup>
4	48	Same	78	44	55	23	22	6.5

A - previous measurement, B - immediate preoperative measurement.

## Original Article

responsible for the worsening of the myocardial function. After the first episode, we started triple immunosuppression with prednisone 0.5 mg/kg/d, which was gradually reduced to 0.1 mg/kg/d after an intravenous pulse for three days.

The third and fourth patients had a single grade II rejection episode each, which was controlled by an oral regimen of prednisone for two months. We also maintained oral anticoagulant in patients 3 and 4, who had late survival, and diuretics, enzyme antagonists and, then, the beta-blocker carvedilol, in order to prevent or delay the progressive myocardial dysfunction of the native heart.

This practice, however, was not successful; on the contrary, the deterioration of the left ventricular function of the native heart was relentless, and even both patients with late survival showed progressive aortic insufficiency with marked clinical worsening, which required surgical correction, as mentioned in the literature<sup>9</sup>.

## Results

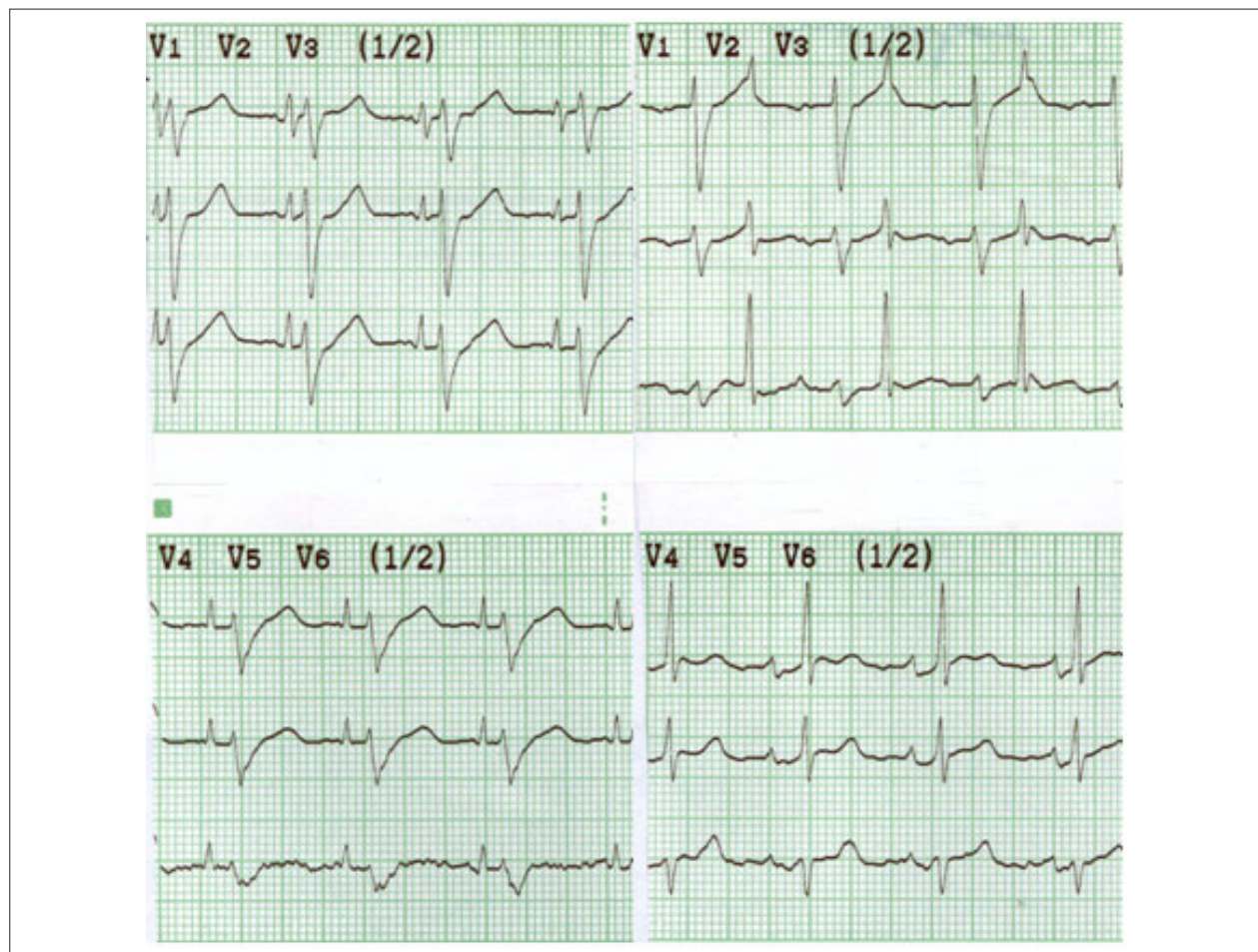
The early and late results of the surgeries are summarized in Table 2. Patient 2 died at the hospital, 12 hours after

transplantation, from graft and native heart failure.

Patient 1 had good evolution in the first year and then showed progressive heart failure, after two episodes of acute rejection and coronary artery disease in the graft. A retransplantation was performed two years after the transplantation, which resulted in death from low cardiac output and acute sepsis on the seventh postoperative day.

Initially the 3<sup>rd</sup> patient had an adequate evolution, with good physical capacity—functional class II (NYHA)—practicing sports, such as swimming, regularly. Figure 2 shows chest X-rays features, with the conventional surgical technique and the new technique developed by the group<sup>5</sup>. In this patient, who underwent the new surgical technique, the pulmonary angiography showed good anatomical and functional results (Figure 3).

The sequential echocardiographic control showed rapid and progressive decline of the ventricular function of the native heart, with a thrombus formation at the end of the first year, which disappeared with the increase in oral anticoagulation. After the sixth year of evolution, there was progressive aortic insufficiency due to anuloaortic ectasia,



**Figure 1** - On the left column, classic precordial leads showing the implanted heart beats and the native heart beats, with large QRS. In the right column, inverse precordial leads, in a different time period, showing the native heart beats and the implanted heart beats. Notice the similar heart rates with no pacemaker resynchronization.

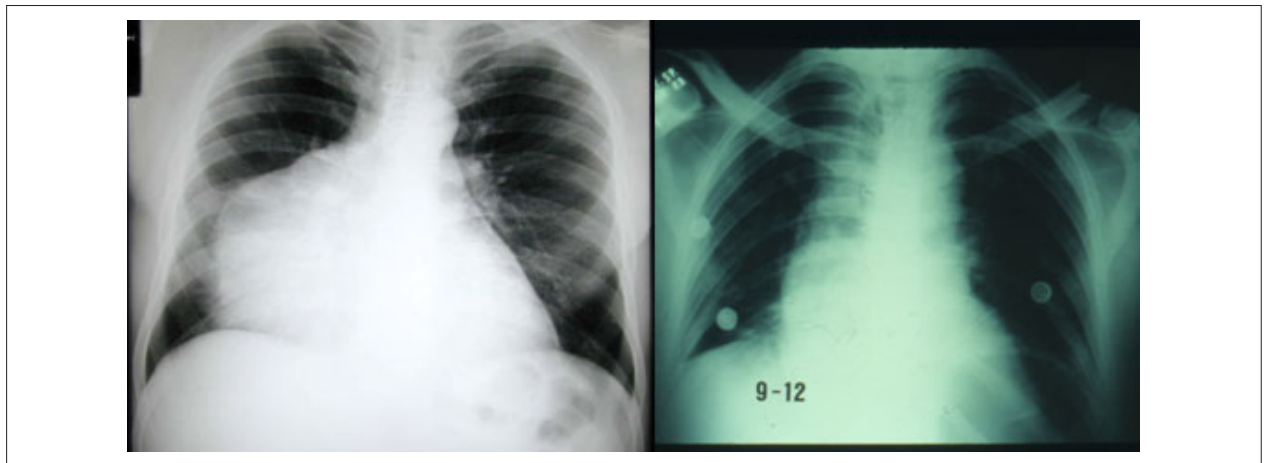
with a deterioration of the clinical conditions, despite the increase in the clinical treatment with enzyme antagonists (captopril), spironolactone, carvedilol and diuretics. We opted for the surgical correction of the aortic valve

insufficiency, which was preferred for technical reasons to the native organ explantation, and this resulted in a significant functional improvement of the patient, who returned to functional class II (NYHA). The ventricular function of the graft in heterotopic position in this patient had always been normal, and there was no significant rejections detected by non-invasive tests, such as myocardial mapping with Gallium and echocardiogram.

The fourth patient, in a very similar manner, also presented a progressive worsening of the left ventricular function of the native heart and received oral anticoagulants from the beginning of the postoperative period. Similarly, aortic valve insufficiency of the native heart occurred, which also required surgery to correct this defect. When the explantation of the native heart was performed, the patient unfortunately had a severe cerebral vascular accident, possibly from thromboembolic origin, and died from infectious complications in the intensive care unit,

**Table 2 – Results**

Patient	Evolution 1	Evolution 2
1	Retransplantation after 2 years due to rejection and coronary disease in the graft	Death from low cardiac output and acute sepsis on the 7th day after the retransplantation
2	In-hospital death	
3	Surgical occlusion of the aortic valve after 6 years	15-year evolution, currently in functional class II (NYHA)
4	Surgical occlusion of the aortic valve after 7 years	Death after 7 years and 4 months



**Figure 2 -** Chest X-rays (PA view) with the conventional technique. At left: with the use of a prosthetic tube; at right: with a direct anastomosis between the pulmonary arteries. Notice in this case the lower compression of the right lung.



**Figure 3 -** Pulmonary angiography using the technique of a direct anastomosis between the pulmonary arteries without the use of a prosthetic tube. There is a good distribution of flow between the two lungs.

with a total survival of 7 years and 4 months after the transplant surgery.

## Discussion

In reviewing our results with orthotopic heart transplantation, we observed that the pulmonary hyperresistance was an important direct or indirect cause of hospital mortality. This is in line with the experience of the Stanford University, which reported a mortality rate of 42% in the first three months, when the receivers' PVR was more than 2.5 WU, despite the use of sodium nitroprusside (Nipride R), and a mortality rate of 25 % for those whose PVR was reduced to less than 2.5 WU with Nipride R, though at the expense of systemic hypotension<sup>10</sup>.

The indications for HetTrx are still controversial, but the patients with PVR between 4.5 and 7 WU benefit from this technique, according to the majority of transplant centers<sup>10,11</sup>. However, in cases of PVR of 7 or more fixed units, a cardiopulmonary transplantation is preferred to the HetTrx because, besides the higher surgical risk, this level of PVR is associated with irreversible and probably progressive anatomical changes in the pulmonary vasculature<sup>1</sup>. In the latter group, a unilateral heart and lung block transplantation is also possible, with the possibility of reverting the anatomical and functional changes in the pulmonary vasculature due to the immediate reduction in the pulmonary pressure and the consequent stimulus for pulmonary vascular reaction<sup>12</sup>.

A more simple, practical and accurate criterium was proposed by the group of Pittsburg<sup>13</sup>, based on the transpulmonary gradient (TPG), which is the difference between the mean pulmonary artery pressure and the mean pulmonary capillary pressure. This study demonstrated that patients with TPG greater than 15 mmHg had higher mortality rates than those with TPG from 10 to 15; the mortality was even lower when the gradient was less than 10 mmHg. Furthermore, this study does not define what is the gradient that renders the cardiopulmonary transplant necessary.

It is not always easy to work based on hemodynamic data as proposed by most authors, especially in Brazil where there is a long delay between the preoperative hemodynamic study and the day when the transplant is performed, which often results in the progression of the vascular lung disease. Therefore, we have routinely used a hemodynamic monitoring with vasodilator drugs on the day of the transplant, in the ICU or in the operating room (before anesthetic induction), using a Swan-Ganz catheter, while we awaited the arrival of the donor. It may be surprising (Table 1) to observe that the 2<sup>nd</sup> patient had 1 WU above the initial preoperative measure. This assessment allows us, in cases of higher PVR, to use pulmonary vasodilator drugs preventively, including via inhalation, and orally, after discharge from the ICU.

In patient 1, we noticed that the PVR was a little less than 5 WU, but the TPG was above 10. The severe clinical evolution of this patient in the last 3 months of waiting stressed the indication for a HetTrx, which was reinforced by the finding of a donor of inappropriate size (weight 15% lower).

As to the new technique, which was used in 3 patients and avoids the use of the Dacron graft between the pulmonary

arteries, it represents the first major innovation in the last 20 years and has the advantages of preventing the theoretically possible complications with the artificial graft (infection, thrombosis, pulmonary embolism and obstruction by fibrous panus), and it also facilitates the endomyocardial biopsy, because the anastomosis of the cava superior easily leads the biopsy forceps to the RV of the transplanted heart<sup>5</sup>.

As to the late results, the HetTrx showed lower survival than the orthotopic transplantation (one-year actuarial survival of 61.4%, and 56% for 2 years), but this comparison is valid only as an information source, since the HetTrx patients have different clinical characteristics in comparison to the orthotopic heart transplantation patients<sup>14</sup>.

In this small experiment, we observed that the patients with global cardiomyopathy, involving also the RV, as our patient 2, suffer higher risk during surgery, because the receiver's diseased RV would have to maintain the pulmonary circulation after the aortic clamping, which is usually long, during the transplantation. Beyond this more immediate risk, there is the problem of progression of the cardiomyopathy, which made the presence of this heart disadvantageous due to potential complications. However, the patients who have ischemic cardiomyopathies that are restricted to the LV, with only RV hypertrophy, as in cases 1, 3 and 4 of our experience, are ideal candidates, because they will have a better initial performance, and their RV will perform well its role of overcoming the high PVR.

However, in patients 3 and 4, the long-term follow up demonstrated the complications mentioned in the literature<sup>15,16</sup>, mainly progressive deterioration of the left ventricular function and aortic insufficiency due to severe anuloaortic ectasia, in the native heart. This latter complication required corrective surgery in the third patient 6 years ago, resulting in better clinical conditions, with the exclusion of the native heart from circulation, which was maintained satisfactorily by the implanted heart, and the patient was in good clinical conditions, 15 years after surgery. In the fourth patient, during the surgical correction of the aortic valve insufficiency, an attempt of total explantation of the native heart was complicated by an episode of severe stroke, and the patient died at the hospital.

The causes of progressive ventricular dysfunction in the native heart could be summarized as follows: 1) Progression of myocardial disease, due to arrhythmias and progression of coronary disease in the native heart; 2) elevation of the post-load due to dyssynchrony of the implanted heart with the native heart, which may lead to the simultaneous occurrence of heart beats, determining an important elevation of the impedance during the systole of the diseased heart; 3) anulo-aortic dilatation by the mechanisms mentioned above, determining progressive aortic insufficiency<sup>9</sup>.

Cowell et al<sup>17</sup> and Morris-Thurgood et al<sup>18</sup> demonstrated that the synchronization of the beats of both hearts by pacemaker, using the classical principle of the intra aortic balloon, or else, the contraction of the native heart by its atrial frequency, leading the atrial and ventricular contraction of the implanted heart, after the closing of the aortic valve of the native heart, could prevent the complications arising from the increased impedance to the ventricular output of the native heart. As a

result, this could lead to a better functional preservation of the left ventricle of the native heart and perhaps the prevention of valve dysfunctions of the organ.

In conclusion, this experience with heterotopic heart transplantation was illustrative, because despite a late survival of 15 years, with the patient in good condition, even in this case, a surgical procedure for functional exclusion of the native heart was necessary. The other patients died, one at hospital, other two years after surgery, and the remaining 7 years after surgery. We believe, however, that the progressive ventricular dysfunction in the native heart, and the annulo-aortic ectasia and its consequent aortic insufficiency could be postponed by the employment of permanent synchronization by pacemaker, which was not used at the time in our patients. With it, this procedure could compare itself favorably with, for instance, cardio-pulmonary transplantation, another option for the

treatment of patients with high PVR, in which a survival of 15 years is peculiarly rare<sup>19-20</sup>.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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### Study Association

This study is not associated with any post-graduation program.

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